Inversions of Both Adjacent Centers in the Formolysis of a 2,2,6-Trialkylcyclohexyl Tosylate. Formation of a 13α-D-Homo Steroid[1]

FRIEDA B. HIRSCHMANN AND HANS HIRSCHMANN*

Department of Medicine, University Hospitals and Case Western Reserve University, Cleveland, Ohio 44106

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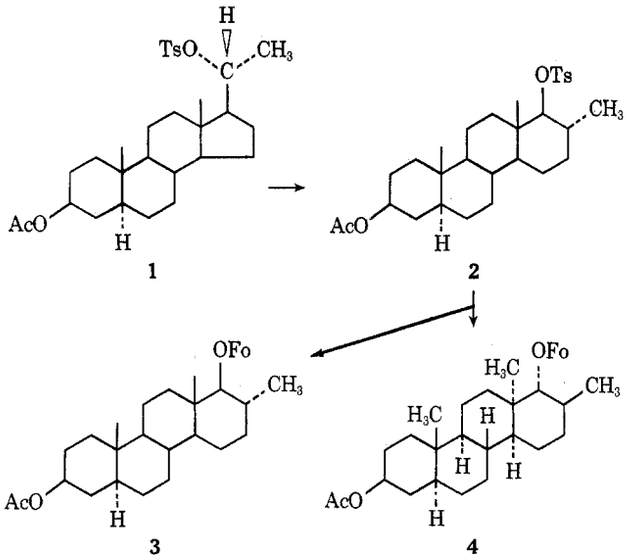
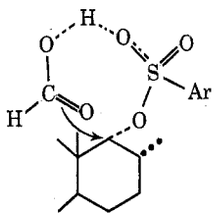
A side product (**4**) obtained from the formolysis of 3β-acetoxy-5α-pregnan-20β-yl tosylate (**1**) or of 3β-acetoxy-17α-methyl-*D*-homo-5α-androstan-17aβ-yl tosylate (**2**) has been identified by partial synthesis and nmr spectroscopy as 3β-acetoxy-17β-methyl-*D*-homo-5α,13α-androstan-17aα-yl formate. The parent diol of **4** was prepared from 3β-acetoxy-5α,13α-androstan-17-one by a series of steps which included cleavage of the D ring, elongation of the longer chain by two carbon atoms, recyclization, and hydrogenolysis. Conceivable mechanisms for the extraordinary inversions at C-13 and C-17 during the formolysis of **2** are discussed. These would also account for the unusual course of the main reaction which converts **2** to the 17a-formate **3** with retention of configuration and preservation of the carbon skeleton.

The conversion of a 20β-tosyloxypregnane (**1**) to a 17aβ-formoxy-17α-methyl-*D*-homoandrostane (**3**) upon reaction with formic acid occurs in two stages.[2] The first is the rapid formation of the corresponding 17aβ-tosyloxy-17α-methyl-*D*-homoandrostane (**2**), which slowly gives the final product (**3**). The second



step was unexpected, as it represented a substitution reaction without change of the configuration or of the carbon skeleton. Retention of configuration seemed explicable if the approach of solvent from the α side were unduly restricted. There was no evidence[2] that this was the case, and more recent demonstrations of inversions of 17aβ derivatives in displacement reactions[3,4] cast further doubt on the validity of such an explanation. Moreover, a 17a carbocation would be adjacent to a carbon with four alkyl substituents and therefore be prone to a Wagner–Meerwein rearrangement. Alternatives to an ionization yielding a C-17a cation, therefore, had to be considered. An attack on the S–O instead of the C-17a–O bond of the tosylate could be disproved for the acetolysis and an alcoholysis[2] and is, therefore, most improbable for the formolysis. Leboeuf, *et al.*,[4] have more recently proposed an SNi process with a cyclic transition state (**5**), which we consider an equally implausible mechanism.[5] Another explanation would be the formation of a carbocation other than the open C-17a cation. In our earlier report[2] we mentioned two bridged ions (**23**, **24**) as possible intermediates, either of which would account for the retention by a double inversion. As the structure of the ionic intermediate might be revealed by those of the side products of the formolysis, we have sought to identify a compound previously characterized by its ir and nmr spectra as another acetate formate (**4**).[2] It was obtained by formolysis of either 3β-acetoxy-5α-pregnan-20β-yl tosylate (**1**)[2] or of 3β-acetoxy-17α-methyl-*D*-homo-5α-androstan-17aβ-yl tosylate (**2**) in comparable yield (2%). We have now established its rather unusual structure, which is that of 3β-acetoxy-17β-methyl-*D*-homo-5α,13α-androstan-17aα-yl formate (**4**).



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The most revealing feature of its nmr spectrum (Table I) was the signal of the proton linked to the carbon atom to which the formoxy group is attached. This signal was observed as a doublet at 5.09 ppm with a

(1) Supported by U. S. Public Health Service Grants AM 9105 and K6-AM-14367.

(2) H. Hirschmann, F. B. Hirschmann, and A. P. Zala, *J. Org. Chem.*, **31**, 375 (1966).

(3) R. T. Li and Y. Sato, *ibid.*, **33**, 3635 (1968).

(4) M. Leboeuf, A. Cavé, and R. Goutarel, *Bull. Soc. Chim. Fr.*, 2100 (1969).

(5) As the stabilization provided by a hydrogen bond is not very large and as an eight-membered cyclic transition state on the β facet of C-17a would encounter and cause major steric compressions and distortions, it seems dubious whether **5** can be significantly more favorable than the transition state of an SN2 process with retention for which no example appears to be known [N. L. Allinger, J. C. Tai, and F. T. Wu, *J. Amer. Chem. Soc.*, **92**, 579 (1970)]. Although some regard the conversion of a chloro sulfite to a chloride of the same configuration as the intramolecular analog of this process, doubts have been expressed in this postulate of a nonionic mechanism. [Streitwieser ("Solvolytic Displacement Reactions," McGraw-Hill, New York, N. Y., 1962, p 158) has reviewed the evidence indicative of an ionization yielding pairs of the carbocation first with the chloro sulfite and then with the chloride ion.] Similar objections must be raised in the present case. Although precise measurements are lacking, it is evident that the solvolysis of a 17aβ tosylate in methanol[4] or acetic acid[2] is slow compared to that in formic acid.[2] Relative to equatorial *trans*-4-*tert*-butylcyclohexyl tosylate [S. Winstein and N. J. Holness, *J. Amer. Chem. Soc.*, **77**, 5562 (1955)], which on acetolysis yields practically no 4-*tert*-butylcyclohexyl acetate of retained configuration [N. C. G. Campbell, D. M. Muir, R. R Hill, J. H. Parish, R. M. Southam, and M. C. Whiting, *J. Chem. Soc. B*, 355 (1968)], the 17aβ tosylate reacts somewhat faster in formic acid (25°)[2] and somewhat slower in acetic acid (100°)[2]. There is no indication, therefore, that in going from the cyclohexyl tosylate to the steroid the role of formic acid changes from a solvating agent for developing ions to one that acts primarily as a nucleophile, as would be expected if **5** represented the transition state.

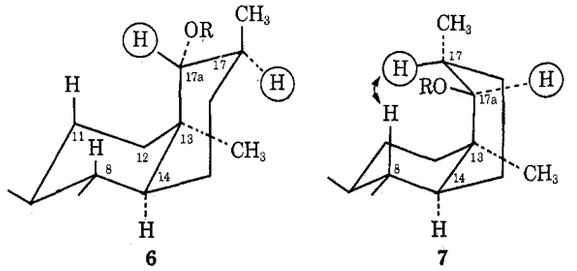
Table I

Nmr Signals of 3β-Acetoxy-17-methyl-D-homo-5α-androstan-17a-yl Esters[a]

Configuration at C-13	α	β	β	
Substituent at C-17a				
FoO (4)	AcO (19b)	FoO (3)	AcO	Assignment
1.00	0.98	0.87	0.85	18-H
0.85	0.85	0.79	0.79	19-H
0.87 (d, 6)	0.84 (d, 6.3)	b	0.79 (d, 6)	17-Me
2.01	2.01	2.00	2.00	3-Ac
	2.05		2.05	17a-Ac
5.09 (d, 10)	4.97 (d, 10.7)	4.42 (d, 11)	4.33 (d, 10)	17a-H
8.18		8.18		Fo

[a] All compounds have equatorial orientations of their substituents at C-17 and C-17a (*i.e.*, 17β,17aα in the 13α and 17α,17aβ in the 13β series). All signals listed are singlets except those marked d. Chemical shifts are in parts per million from TMS; the coupling constants of the doublets (in cycles per second) are given in parentheses. [b] Not resolved.

coupling constant of 10 cps. This indicated the partial structure $C_3CCH(OCHO)CHC_2$ with a dihedral angle of about 180° between the two vicinal C–H bonds. Like the main reaction product **3**, the compound contained two tertiary methyl groups (with singlets at 0.85 and 1.00 ppm) and a secondary methyl giving rise to a doublet at 0.87 ppm. As such a structure had to be derived from **2**, it probably represented a stereoisomer of uranediol acetate formate (**3**). If it had an all-chair conformation and if the configurational changes were confined to the vicinity of the reaction site, **4** had to be isomeric at both C-13 and C-17 in order to accommodate the coupling constant of the doublet at 5.09 ppm (**6**).



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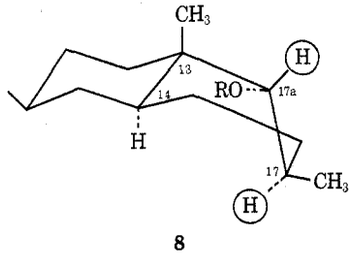

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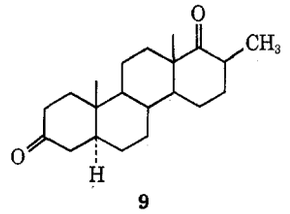

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R=H or HCOO

Only if we make the rather unlikely assumption that a 1,3-diaxial interaction between two methyl groups could be strong enough to force the D or the C ring into a boat, would inversion at either C-13 (**7**)[6] or C-17 (**8**) also be consistent with the coupling phenomenon. The trans relationship of the coupled protons further requires that an inversion at C-17 be accompanied by one at C-17a. Therefore, **7** is a 17aβ formate like **3** whereas **6** and **8** have the 17aα configuration. Structure **8** was readily excluded because conversion of the isolated acetate formate to the diketone gave a product distinct from a sample of 17-epiuranedione (**9**) prepared by the method of Fukushima, *et al.*[7] As the two remaining structures under consideration were both 13α-D-homo steroids, we set out to prepare such compounds to identify, if possible, the solvolysis product by comparison with a 13α compound of proven structure.

The irradiation of 17-oxo steroids affords ready access to their 13 epimers.[8] As these have been found to be less reactive or unreactive in several addition reactions to their 17-keto group,[8] it was not too surprising that we had no success in converting 3β-acetoxy-5α,13α-androstan-17-one (**10**)[9] to its cyanohydrin, which was required for applying the Goldberg procedure for D-homoannulation.[10] We were also unable to enlarge the D ring by treating **10** with diazomethane[11] in the presence of boron trifluoride and abandoned these trials in favor of the scheme that is outlined in Chart I.

The D ring of **10** was cleaved by a procedure which we had used previously with 3β-hydroxy-5α-androstan-17-one.[12] Oxidation of the purified or crude acetoxybenzylidene compound **11b** with chromic acid in acetic acid gave two degradation products in comparable amounts. Of these, the desired 16,17-dioic acid was recovered partly and its lower homolog predominantly as the anhydride (**12** and **13**, respectively) from the neutral fraction of the reaction mixture.[12a] These compounds were readily differentiated by their ir spectra, which showed the characteristic twin peaks of anhydrides in the carbonyl region at frequencies typical of six- and five-membered rings.[13a] The homologs were separated by chromatography after the essentially complete conversion of the reaction products to anhydrides. Compound **12** yielded the dimethyl ester **14**[14] on hydrolysis, treatment of the dioic acid with diazomethane, and reacetylation. Hydrolysis with

(6) This structure is particularly improbable because the bow–stern interaction which is between a methine carbon (C-8) and a hydrogen is larger than usual. If instead ring C were a boat (not shown), a comparable interaction would exist between C-18 and 9α-H.

(7) D. K. Fukushima, S. Dobriner, and R. S. Rosenfeld, *J. Org. Chem.*, **26**, 5025 (1961).

(8) A. Butenandt, A. Wolff, and P, Karlson, *Chem. Ber.*, **74**, 1308 (1941); A. Butenandt and L. Poschmann, *ibid.*, **77**, 394 (1944).

(9) (a) J. R. Billeter and K. Miescher, *Helv. Chim. Acta*, **34**, 2053 (1951); (b) M. Fétizon and J. C. Gramain, *Bull. Soc. Chim. Fr.*, 3444 (1966); 1003 (1967); (c) T. Nambara, H. Hosoda, and M. Usui, *Chem. Pharm. Bull.*, **17**, 1687 (1969).

(10) M. W. Goldberg and R. Monnier, *Helv. Chim. Acta*, **23**, 376 (1940).

(11) C. D. Gutsche, *Org. React.*, **8**, 364 (1954); H. O. House, E. J. Grubbs, and W. F. Gannon, *J. Amer. Chem. Soc.*, **82**, 4099 (1960).

(12) H. Hirschmann, *J. Biol. Chem.*, **150**, 363 (1943).

(12a) Note Added in Proof.—The formation of a lower homolog which we had not observed in 13β series may be due to the tendency of 16,17 diketones to enolize if there is a cis junction of the C and D rings [L. J. Chinn, *J. Org. Chem.*, **29**, 3304 (1964)].

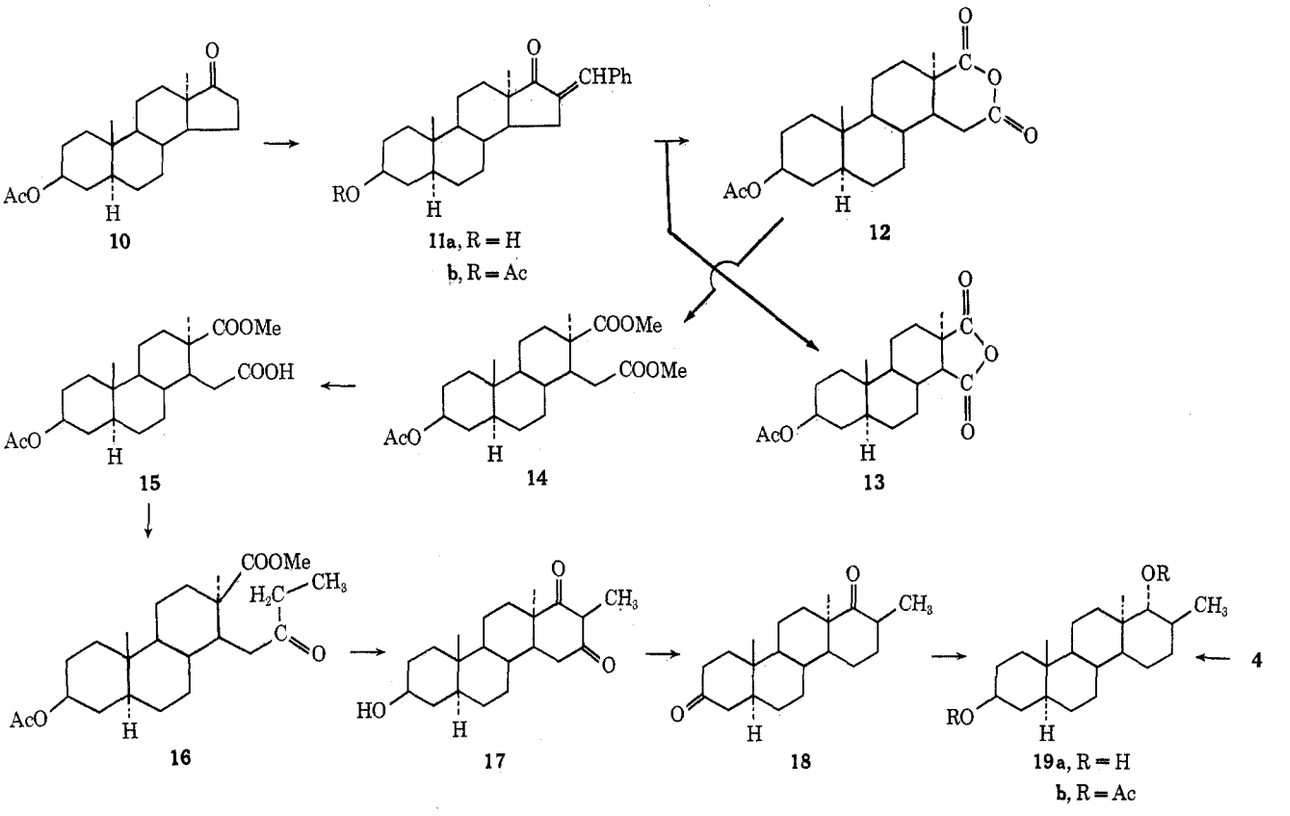
(13) L. J. Bellamy "The Infra-red Spectra of Complex Molecules," Methuen, London, 1954: (a) p 110; (b) p 123.

(14) Attention should be directed to the unexpectedly high frequency of a conspicuous band which was observed at 3018 cm^{-1} in **14**. It was also seen (3016–3018 cm^{-1}) in other saturated methyl esters (**15**, **16**, and two independent preparations[15] of methyl 3β-hydroxy-5α-etianate and of methyl 3β-acetoxy-5α-etianate) but was absent from the curves of the anhydrides **12** and **13**.

(15) F. B. Hirschmann, D. M. Kautz, S. S. Deshmane, and H. Hirschmann, *Tetrahedron*, **27**, 2041 (1971).

CHART I

SYNTHESIS OF 13α-D-HOMO STEROIDS



sodium carbonate[16] followed by reacetylation gave the 17-monomethyl ester **15**. It was converted to its acid chloride,[17] which afforded the ethyl ketone **16** on reaction with diethylcadmium. Cyclization of **16** with sodium hydride in benzene gave poor and erratic results, but high yields of **17** were obtained consistently when the solvent was changed to dimethyl sulfoxide.[18] The product had the characteristics of an enolizable β diketone. It could be extracted from ether with aqueous sodium carbonate. In ethanol the enolic tautomer or tautomers predominate, as shown by an intense peak at 266 nm.[19] The final crystals, when examined in the ir, had only the peaks characteristic of enolic forms (2684 and 1599 cm^{-1}).[13b,20] The ir curves of other preparations, however, indicated the presence also of the dioxo form, which may be presumed to have the more stable β configuration at C-17.

The unwanted oxygen at C-16 could be removed by hydrogenolysis on platinum, but this process was accompanied by hydrogenation. The latter became evident on oxidation of the mixture of neutral reaction products, as this step regenerated some enolic material. The products which remained insoluble in carbonate were fractionated by chromatography. The main crystalline component (**18**) showed two well-resolved peaks in the carbonyl region of the ir. The complete spectrum matched the one we had obtained for the oxidation product of the diol derived from formate **4** (see above). If we consider the partial structure deduced for **4** from the nmr signal at 5.09 ppm, it follows that hydrogenolysis had removed the oxygen function at C-16 and not at C-17a. Conversely it follows from the synthesis of **18** from **10** that **4** is a 13α-D-homo steroid. The spectrum of the synthetic 3,17a diketone remained unchanged upon treatment with alkali under conditions that caused the inversion at C-17 in an analog of **9**.[7] We conclude that the 17-methyl group of **18** has the stable (equatorial) β orientation and we can make the same assignment for **4** unless an inversion to the more stable configuration occurred during the oxidation. This unusual event (*cf.* footnote 18 of ref 2) can be excluded if it is possible to prepare the parent diol of **4** by reduction of **18**.

To obtain **19a** from **18**, the hydrogen which has to be added to the 17a-carbonyl is axial and in syn-axial interaction with both C-11 and C-8 (6). The steric hindrance of the axial approach could, therefore, be expected to be comparable to that encountered in the reduction of an 11 ketone to the 11α-ol. As the only effective procedure for this conversion is reduction by a metal–proton donor combination, we treated **18** with sodium in propanol after a trial experiment with 5α-cholestan-3-one had shown that the reduction of its 3-

(16) (a) E. B. Hershberg, E. Schwenk, and E. Stahl, *Arch. Biochem.*, **19**, 300 (1948); (b) H. M. E. Cardwell, J. W. Cornforth, S. R. Duff, H. Holtermann, and R. Robinson, *J. Chem. Soc.*, 361 (1953).

(17) Procedure of A. L. Wilds and C. H. Shunk, *J. Amer. Chem. Soc.*, **70**, 2427 (1948).

(18) J. J. Bloomfield, *J. Org. Chem.*, **27**, 2742 (1962).

(19) This is close to the expected wavelength. The peak observed for 1,3-dioxo-5β steroids is 256–257 nm in alcohol [data by C. Tamm quoted by J. J. Schneider, P. Crabbé, and N. S. Bhacca, *ibid.*, **33**, 3118 (1968)]; the increment expected for methyl substitution on the α carbon of similar β diketones was estimated by E. G. Meek, J. H. Turnbull, and W. Wilson, *J. Chem. Soc.*, 2891 (1953), to be about 8–9 nm.

(20) As such uv and ir bands have been attributed to conjugated chelation [R. S. Rasmussen, D. D. Tunnicliff, and R. R. Brattain, *J. Amer. Chem. Soc.*, **71**, 1068 (1949)], it should be noted that the cyclic dimeric structure which has been postulated for derivatives of 1,3-cyclohexanedione by Rasmussen, *et al.*, appears to be sterically impossible in our case. However, a larger cycle, such as a tetramer, can be constructed without excessively long hydrogen bonds or unduly close distances between nonbonded atoms.

keto group under these conditions gives a very high preponderance of the equatorial alcohol. The reduction of **18** afforded **19a** in good yield. It was identical with the hydrolysis product of **4**,[21] as was shown by comparisons of the melting points and ir spectra of the diols and their diacetates. These identities show that the compound we have isolated from the formolysis products of **1** and **2** has a structure that conforms in all particulars to the one depicted in formula **4**.

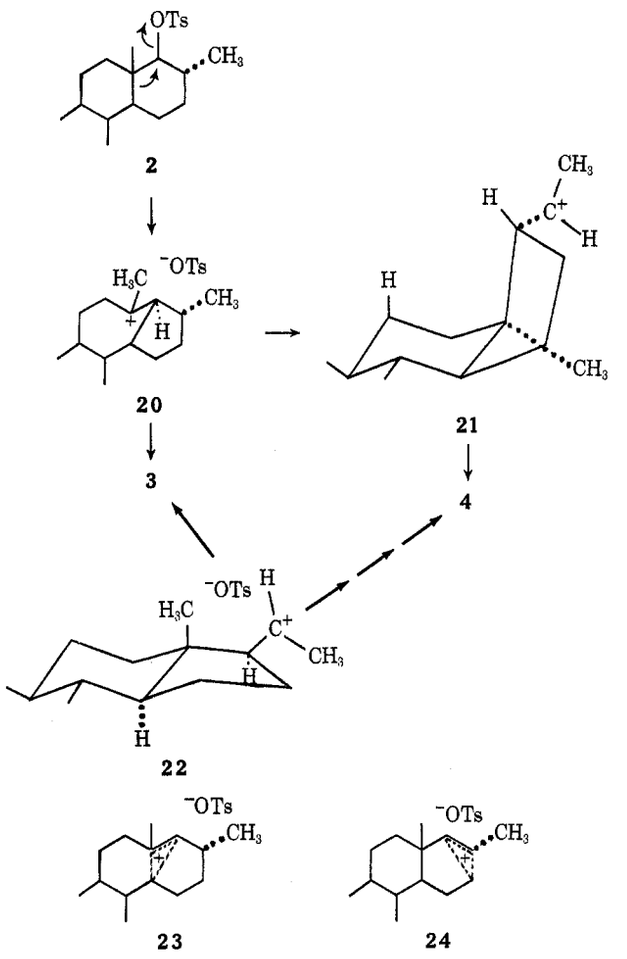
Comparison of the nmr spectra of **4**[2] and **19b** with those of the corresponding 17a formate (**3**) and 17a-acetate of uranediol 3 acetate[2] suggests the assignment of signals given in Table I. The attribution of the peak near 1 ppm to the 18- rather than to the 19-methyl of **4** and **19b** seems to fit better with observations on the effect of inversion at either C-10 or C-13 of 5α-androstane. These inversions caused a downfield shift (0.23 or 0.17) in the signal of the inverted methyl and a smaller upfield change (0.005 or 0.08 ppm) for the methyl that retained its orientation.[9b] The tabulated results further show that the only large difference between the two stereoisomeric series of D-homo steroids is the shift in the signal of the 17a-H.

Discussion

Formate **4** differs from the starting compound **2** or from its main formolysis product **3** in the configurations of three centers, C-13, C-17a, and C-17. To account for this unusual reaction one can envisage two basically different processes. The first would involve migration of the methyl groups. As there appears to be no precedent for the crossing of the plane of a ring when a methyl group is transferred to an adjacent carbon atom, inversion by methyl migration would seem to be possible only if there is an exchange of the methyl groups at C-13 and at C-17. This in turn appears to require a 1,3 shift of one of these groups. Although such a step cannot be dismissed *a priori*, it seems justified to give preference, at least initially, to mechanisms that involve only the much more common 1,2 migrations. Accordingly, we shall limit this discussion to pathways in which the methyl groups remain stationary.

To allow for the inversion of C-13 in such a scheme, this center must assume a planar configuration at some intermediate stage. A suitable structure is shown in **20** (Chart II). It is attractive to picture its formation from **2** as a concerted process, as this would place the reaction in close analogy to the ionization of an equatorial mesylate group at C-12.[22] The completion of the inversion process requires the restoration of the bond between C-13 and C-14. This step may be thought to be facilitated if a new bond forms at the site of the developing charge (C-17a). This would be demanded by the principle of microscopic reversibility if there is an internal return to **2** and if the forward reaction has been correctly formulated as a concerted process. It, therefore, seems a plausible mechanism also for the conversion of **20** to **3**. In contrast a concerted process analogous to **20** → **2** but leading to a 17a tosylate with the 13α configuration is not a likely event.

Chart II



Unless the C ring has a particularly unfavorable boat conformation,[6] an entry of the tosylate ion, antiparallel to the displaced C-14–C-17a bond of **20**, is possible only if the product were the 13α,17aα isomer of **2**. Its formation from **20**, however, would require a change in the orientation of the 17a-hydrogen from α to β across the path of the incoming tosylate ion. The net result would constitute a retention of configuration and, therefore, ought not occur in a single step. In contrast an attack of the 16–17 bond on C-17a to yield **21** would represent an inversion.[23] This 13α,17α-pregnan-20-yl ion is shown in **21** in its favored conformation with the methyl group above the hydrogen. A reversal of the latter bond shift with equatorial entry of the solvent would lead to the isolated product (**4** ≡ **6**).

We have also considered a similar scheme which would start rather than end with the inversion of C-17 of **2**. Although a precedent seems to exist for the shift of the 16–17 bond toward C-17a in certain rearrangements of 17,17a-D-homo ketols,[24] we regard a sequence beginning

(21) Any conceivable doubts about the 3β configuration of **19a** are dispelled by this identity and by a second synthesis from the 3 acetate of **17**, in which no oxidation occurred at C-3.

(22) R. Hirschmann, C. S. Snoddy, Jr., C. F. Hiskey, and N. L. Wendler, *J. Amer. Chem. Soc.*, **76**, 4013 (1954).

(23) As the geometry is not too favorable, it seems uncertain whether both bond shifts would occur simultaneously, or in rapid succession to relieve the syn-axial interaction of methyl groups of an intermediate 17α-methyl-D-homo-13α-androstan-17a-yl cation. The preferential formation of the 17α isomer (**21**) can be expected by either mechanism because as judged from models and from studies of 13α-pregnan-20-ones [T. Nambara and J. Goto, *Chem. Pharm. Bull.*, **19**, 1937 (1971)] the α isomer at C-17 is more stable than the β.

(24) N. L. Wendler, D. Taub, and R. W. Walker, *Tetrahedron*, **11**, 163 (1960).

with the ion pair **22** as a less likely pathway toward formate **4**.[25]

The formolyses of **2** and of its 17a epimer[2] were shown to take wholly different courses. The scheme presented for the formation of **3** and **4** is consistent with this high degree of steric control and would account for the formation of these two products by a common first step. These suggestions would avoid the problems mentioned in the introduction, as the formation of **3** from **2** would represent two successive inversions if it proceeds *via* **20** or **22**. Although this would be equally true if the initially formed ion had the nonclassical structure **23** or **24**,[2] these would be expected to retain their configuration at C-13 and C-17 in an attack on C-17a and, therefore, would fail to explain the formation of **4**. The elucidation of its structure and the hypothesis that there is a common cause of the unusual aspects of the conversion of **2** to **3** and **4**, therefore, would limit the choice of pathways to the main product and suggest new tests for the mode of its formation.

Experimental Section

General Procedures.—Melting points reported are corrected. Rotations were measured on solutions in $CHCl_3$ in a 1-dm tube on a Perkin-Elmer polarimeter (Model 141). Ir spectra were recorded on solutions in CS_2 except for **17** and **19a**, which were examined as KBr pressings. Except when noted otherwise, these were obtained by adding a solution of the steroid in a small volume of methanol to the ground KBr. This mixture was dried *in vacuo*, ground, and pressed. The instrument was a Perkin-Elmer grating photometer, Model 421. The peaks listed are those characteristic of functional groups and other prominent bands. Uv spectra were measured on a Beckman spectrophotometer with a photomultiplier. Nmr spectra were recorded for solutions in $CDCl_3$ containing TMS on a Model HA-100 of Varian. Data are given as shifts in parts per million downfield from TMS.

Neutral steroids were usually isolated from the diluted reaction mixture by extraction with ether or benzene. These extracts were washed (when appropriate) with dilute hydrochloric acid, sodium carbonate, and water and were taken to dryness *in vacuo*. Chromatography was usually done on 2:1 mixtures of silica gel (Merck-Darmstadt, finer than 200 mesh) and Celite, washed as described.[15]

3β-Hydroxy-16-benzyliden-5α,13α-androstan-17-one (11a).—3β-Acetoxy-5α,13α-androstan-17-one (**10**)[9] [mp 135.5–137°; $[\alpha]^{29}$ −97° (589 nm), −115 (546), −205 (436), −361 (365); nmr 0.67 (19-H), 0.97 ppm (18-H)] was prepared essentially as described.[9a] To its solution in methanol (827 mg in 30 ml) were added 5.5 ml of sodium methoxide in methanol (from 266 mg of sodium) and 0.55 ml of freshly distilled benzaldehyde (in two portions). The mixture was heated under reflux for 2 hr. The neutral product (1.12 g) was isolated by ether extraction and repeatedly recrystallized from dilute acetone: mp 109–113.5°; ν_{max} 3609, 1715, 1630, 1128, 1035, 689 cm^{-1}. The mother liquors were chromatographed and recrystallized to similar melting point, yield 748 mg.

Anal. Calcd for $C_{26}H_{34}O_2$: C, 82.49; H, 9.05. Found: C, 81.81; H, 9.22.

3β-Acetoxy-16-benzyliden-5α,13α-androstan-17-one (11b).—A solution of 203 mg of **11a** in 2 ml of pyridine and 1 ml of acetic anhydride was kept at room temperature for 16 hr. The excess of anhydride was hydrolyzed by slowly adding water to the chilled solution. The product was isolated by ether extraction and the neutral material (228 mg) was recrystallized from 95% ethanol. The melting point (67–77°) of **11b** (which retained solvent when dried at room temperature) could not be sharpened by continued recrystallization: ir 1736, 1716, 1631, 1239, 1129, 1029, 689 cm^{-1}.

Anal. Calcd for $C_{28}H_{36}O_3$: C, 79.96; H, 8.63. Found: C, 79.13; H, 8.78.

(25) Tentative assessment based on the results with the 20α tosylate.[16] We hope to obtain a more definitive basis for evaluating this alternative route by studying the formolysis of the 17 epimer of **2**.

3β-Acetoxy-16,17-seco-5α,13α-androstane-16,17-dioic Acid Anhydride (12).—A solution of the acetoxybenzylidene compound **11b** (1.8 g, obtained from 1.32 g of **10** by the steps described but without purifying either **11a** or **11b**) in 295 ml of acetic acid was heated to 73° and maintained at this temperature for 30 min after a solution of CrO_3 (3.77 g) in 52 ml of 90% acetic acid (73°) had been added. The cooled solution was treated with 25 ml of methanol. After 1 hr most of the solvents was removed *in vacuo* and the residue was distributed between dilute hydrochloric acid and ether. The ether phase was washed with water and taken to dryness. The residue (1.79 g) was kept in 5 ml of pyridine and 2.5 ml of acetic anhydride overnight. The solution was distributed between ether and water. The phases were shaken repeatedly and separated after 2 hr. The material in ether was partitioned into an acidic (0.41 g) and neutral fraction (1.14 g). The latter was dissolved in benzene and chromatographed on 114 g of silica gel–Celite. Elution with benzene containing 1% ether gave first 3β-acetoxy-16,17-seco-16-nor-5α,13α-androstane-15,17-dioic acid anhydride (**13**) (25%), then **12** (25%), and elution with methanol gave the remainder as free acids. These were converted to their anhydrides, which on chromatography afforded 9% of **13** and 26% of **12**.

The anhydride fractions with peaks at 1860 and 1791 cm^{-1} (**13**) were recrystallized from acetone–petroleum ether (bp 60–70°): mp 141.5–142.5°; ester peaks at 1736, 1239, and 1030 cm^{-1}.

Anal. Calcd for $C_{20}H_{28}O_5$: C, 68.94; H, 8.10. Found: C, 69.13; H, 8.10.

The anhydride fractions with peaks at 1805 and 1765 cm^{-1} (**12**) were recrystallized from acetone: mp 219–221.5°; ester peaks at 1736, 1239, and 1032 cm^{-1}.

Anal. Calcd for $C_{21}H_{30}O_5$: C, 69.58; H, 8.34. Found: C, 69.78; H, 8.22.

Separations of the anhydrides with far less hydrolysis were obtained initially with an old batch of silica gel (Davison) but these results could not be duplicated with their present product. The ratio **12**:**13** was slightly lower when the oxidation was conducted at lower temperature (70°, 30 min; 65°, 120 min) and markedly lower when acid (H_2SO_4) or base ($NaHCO_3$) were added to the medium.

Dimethyl 3β-Acetoxy-16,17-seco-5α,13α-androstane-16,17-dioate (14).—A solution of 221 mg of the acetoxy anhydride **12** in 48 ml of 90% methanol containing 2% of KOH was kept at room temperature for 2 hr and partitioned into a neutral (0.8 mg) and acidic fraction (226 mg). The latter in 1.5 ml of methanol was treated with an excess of diazomethane in 10 ml of ether. The residue on distribution between ether and sodium carbonate gave 235 mg of neutral and 0.3 mg of acidic products. The neutral fraction was acetylated and the product (253 mg) was recrystallized from petroleum ether. The dimethyl ester (**14**) had mp 99–100°; the carbonyl peak (1736 cm^{-1}) was not resolved; acetate bands at 1241, 1030 cm^{-1}.

Anal. Calcd for $C_{23}H_{36}O_6$: C, 67.62; H, 8.88. Found: C, 67.86; H, 8.95.

The same procedure was carried out with the mother liquors of the anhydride. Thus from 282 mg of chromatographically purified **12**, 279 mg of **14** were obtained.

Methyl 3β-Acetoxy-16-ethyl-16-oxo-16,17-seco-5α,13α-androstan-17-oate (16).—A mixture of 267 mg of dimethyl ester **14** in 35 ml of methanol and 2 g of potassium carbonate in 7.8 ml of water was heated under reflux for 12.5 hr and kept at room temperature overnight. The product, after the removal of methanol *in vacuo*, was separated into a neutral (3 mg) and acidic (228 mg) fraction. The latter was acetylated at room temperature with 4 ml of pyridine and 2 ml of acetic anhydride. The product **15**, which was free (ir) of mixed anhydrides,[16b] failed to crystallize. It was neutralized in methanol with aqueous sodium hydroxide. The dry sodium salt (272 mg) was suspended in 15 ml of dry benzene containing 7 drops of pyridine. Oxalyl chloride (2.5 ml) was added to the chilled mixture, which was kept at 0° for 8 min and at 15° for 15 min. Solvents were removed *in vacuo* (bath temperature <15°) and again after the addition of dry benzene. The residue in 7.5 ml of benzene[26] was added dropwise to a stirred solution of diethylcadmium (prepared from ethyl bromide according to the directions of Guenthard, *et al.*[27]) in 15 ml of ether and maintained throughout in an atmosphere of nitrogen. The mixture was heated under reflux for 1 hr and cooled. Water was

(26) J. Cason, *J. Amer. Chem. Soc.*, **68**, 2078 (1946).

(27) H. H. Guenthard, E. Beriger, C. R. Engel, and H. Heusser, *Helv. Chim. Acta*, **35**, 2437 (1952).

added until the evolution of gas ceased. The neutral reaction product (286 mg) was recrystallized from dilute methanol: mp 120–121.5°; ν_{max} 1735, 1732 (main), 1241, 1028 cm^{-1}. Presence of a keto group, indicated by a shoulder at 1718 cm^{-1}, was confirmed by λ_{max} 273 nm (ε 27, 95% ethanol).

Anal. Calcd for $C_{24}H_{38}O_5$: C, 70.90; H, 9.42. Found: C, 70.89; H, 9.44.

The mother liquors on chromatography on silica gel–Celite and elution with benzene containing 2% ether gave additional amounts of **16**. Total yield from **14** was 66%.

3β-Hydroxy-17-methyl-*D*-homo-5α,13α-androstane-16,17a-dione (17).—The reaction was conducted in a stream of dry nitrogen passing through a three-neck flask equipped with magnetic stirrer and a reflux condenser. A dispersion (210 mg) of 57% sodium hydride in mineral oil was freed of the latter by repeated rinsings with petroleum ether. A solution of 150 mg of methyl 3β-acetoxy-16-ethyl-16-oxo-16,17-seco-5α,13α-androstan-17-oate (**16**) in 10 ml of freshly distilled dimethyl sulfoxide was added to the dry powder. The mixture was maintained at 75–78° for 165 min, cooled, and distributed between ether–benzene and hydrochloric acid. The organic phase was extracted with sodium carbonate, which gave on acidification and extraction 123.7 mg of **17**. Recrystallization of the product from methanol and of the material in the mother liquors furnished 114.4 mg (93%) of **17**, mp 222–225°. Continued recrystallization raised the melting point to 225–227°. These crystals had ν_{max} ~3250, ~2684, ~1599 (no other peak in this region),[28] 1379, 1100, 1064, 1045 cm^{-1}; λ_{max} 266 nm [ε 13,420 in 95% ethanol containing 0.1% 1 *N* HCl; in ordinary alcohol there was a second peak at 295 nm (enolate)[30]].

Anal. Calcd for $C_{21}H_{32}O_3$; C, 75.86; H, 9.70. Found: C, 74.66, 74.78; H, 9.84, 9.90.[31]

17β-Methyl-*D*-homo-5α,13α-androstane-3,17a-dione (18).—A solution of freshly prepared compound **17** (59 mg) in 15 ml of acetic acid was shaken with platinum (from 51 mg of Adams dioxide, previously hydrogenated in acetic acid for 3 min) in an atmosphere of hydrogen for 5.5 hr. The product, after removal of the catalyst, was separated into an acidic (7 mg) and neutral (48 mg) fraction. The former (**17**) was reused for further hydrogenations. The neutral fractions from two such experiments (73 mg) in 3.5 ml of acetone were maintained at 10° while 0.25 ml of CrO_3–H_2SO_4 reagent[33] was added. After 4 min the steroids were extracted and separated into an acidic (17 mg) and neutral (47 mg) fraction. (According to its spectrum the former contained enolic 3,16,17a triketone. It gave additional neutral material with platinum and hydrogen.) The neutral oxidation product was chromatographed on 4.7 g of silica gel–Celite. A small crystalline fraction (1.8 mg) was eluted with petroleum ether–benzene (6:4). This had mp 145–147.5° after recrystallization from methanol and ν_{max} 1703, 1128, 996, 968, 842 cm^{-1}. It probably represents **17β-methyl-*D*-homo-5α,13α-androstan-17a-one**. Further elution of the column with benzene containing 2% ether gave 26 mg of eluate, which was recrystallized from methanol to give the 3,17a dione **18**: mp 147–149° and 150.5–152.5° on reheating of the solidified melt; $[\alpha]^{31}$ +63° (589 nm), +80 (546), +189 (436), and +511 (365 nm); ν_{max} 1712 (3-keto), 1704 (17a-keto), 1226, 1127, 963, and 843 cm^{-1}.

Anal. Calcd for $C_{21}H_{32}O_2$: C, 79.70; H, 10.19. Found: C, 79.62; H, 10.18.

A solution of 1.6 mg of **18** in 2 ml of 2.5% methanolic potassium hydroxide was heated under reflux for 2 hr. The ir spectrum of the recovered material was virtually not altered by this treatment.

17β-Methyl-*D*-homo-5α,13α-androstane-3β,17aα-diol (19a).—Sodium (280 mg) was added in portions to a boiling solution of 21 mg of **18** in 4 ml of 1-propanol. The product was isolated after 85 min and had after recrystallization from methanol a double melting point (144 and 153–154°); ν_{max} ~3390, 1046 (probably C-3–O), 1007, 986, 953, 844 cm^{-1}; yield 17.2 mg.

An identical preparation was obtained by acetylation of **17**, partial hydrolysis of the product at 18° with 1 equiv of KOH in methanol (1 m*M*) for 40 hr to the 3-acetate of **17**, hydrogenolysis and oxidation as described for the preparation of **18**, and reduction with sodium in propanol. This route is not recommended, as the 3-acetate of **17** proved to be even more unstable than **17**.

The diacetate (**19b**), prepared with pyridine and acetic anhydride at room temperature (18 hr), had mp 132.5–134°; $[\alpha]^{26}$ −2° (589 nm), −1 (436), +4 (365 nm); ν_{max} 1731, 1242, 1032, 1022 (main), 975, 971, 955, 931, 894, 604 cm^{-1}; nmr δ 4.68 ppm (m, 3α-H) and those listed in Table I.

Anal. Calcd for $C_{25}H_{40}O_4$: C, 74.21; H, 9.97. Found: C, 74.28; H, 10.08.

Isolation and Identification of Compound 4.—3β-Acetoxy-17α-methyl-*D*-homo-5α-androstan-17aβ-yl tosylate (**2**) was prepared from **1** with formic acid as described[2] and recrystallized three times from acetone. The ir spectra of the final crystals and of the third mother liquor agreed with the spectrum of a preparation obtained from **3** by partial hydrolysis and tosylation.[2] A solution of 250 mg of **2** in 10 ml of benzene and 15 ml of acetone was diluted with 225 ml of formic acid and kept at 23° for 24 hr. **3** (150 mg, mp 216–219°) was isolated as described for the formolysis of **1**.[2] The mother liquors (38 mg) were chromatographed from silica gel (old preparation of Davison)–Celite. The eluates (4 mg) just ahead of **3** gave **4**, identified by comparison of its melting point (179–180.5°) and ir spectrum with the sample obtained from **1** which has been characterized previously.[2]

A solution of 5.3 mg of **4** (derived from both **1** and **2**) in 2 ml of 2% methanolic potassium hydroxide was kept at room temperature for 20 hr. The product was recrystallized from methanol. The melting point (142 and 153–155°) was not depressed by admixture with **19a**. The ir spectra (KBr) also agreed. The diol was acetylated to give diacetate with mp 131–134° which was not depressed by admixture with **19b**. The ir spectra agreed. Another aliquot of the diol (2.1 mg) obtained from **4** by reaction with lithium aluminum hydride in ether was oxidized in acetone with 5 μl of CrO_3–H_2SO_4[33] for 5 min at 15°. The ir spectrum of the product was distinct from those of uranedione and of its 17 epimer (**9**), but agreed with that of **18**.

Registry No.—**1**, 38456-46-1; **2**, 5611-68-7; **4**, 38456-48-3; **10**, 13383-12-5; **11a**, 38456-50-7; **11b**, 38456-51-8; **12**, 38456-52-9; **13**, 38456-52-1; **14**, 38456-53-0; **16**, 38456-54-1; **17**, 38456-55-2; **18**, 38456-56-3; **19a**, 38456-57-4; **19b**, 38456-58-5; 17β-methyl-*D*-homo-5α,13α-androstan-17a-one, 38456-59-6.

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(28) This spectrum was observed on a pellet prepared by grinding the crystals of **17** with KBr. Other cruder preparations of **17** which had been incorporated into KBr by adding their solutions in methanol showed in addition to the enol peak near 1600, bands near 1700 and 1720 cm^{-1} (the latter usually as a shoulder) which are presumably due to the 16,17a-dione tautomer.[29] The intensity ratio of these keto and enol bands varied widely.

(29) (a) C. Tamm and R. Albrecht, *ibid.*, **43**, 768 (1960); (b) H. Muehle and C. Tamm, *ibid.*, **45**, 1475 (1962).

(30) For similar observations see B. Eistert and W. Reiss, *Chem. Ber.*, **87**, 108 (1954), and E. R. Blout, V. W. Eager, and D. C. Silberman, *J. Amer. Chem. Soc.*, **68**, 566 (1946).

(31) This analysis was not repeated, as the compound, like other α-alkyl substituted β diketones,[29b,32] decomposed. Broadening of the melting point and increased coloration of the melt were noticeable within 2 days of preparation.

(32) R. B. Woodward and E. R. Blout, *J. Amer. Chem. Soc.*, **65**, 562 (1943).

(33) A. Bowers, T. G. Halsall, E. R. H. Jones, and A. J. Lemin, *J. Chem. Soc.*, 2548 (1953).